AD NUMBER

ADB175882

NEW LIMITATION CHANGE

TO

Approved for public release, distribution unlimited

FROM

Distribution authorized to U.S. Gov't. agencies only; Proprietary Info.; Jul 93. Other requests shall be referred to U.S. Army Medical Research and Development Command, Attn: SGRD-RMI-S, Ft. Detrick, Frederick, MD 21702- 5012.

AUTHORITY

USAMRMC ltr., 21 Apr 97

CONTRACT No. DAMD17-92-C-2081

TITLE: Synthesis of Antidotes and Prophylactics for Organophosphorus Acetylcholinesterase Inhibitors

PRINCIPAL INVESTIGATOR: Richard J. Sundberg
Phuoc Van Nguyen

PI ADDRESS: Department of Chemistry
University of Virginia
Charlottesville, Virginia 22901

REPORT DATE: July 1, 1993

TYPE OF REPORT: Annual Report

PREPARED FOR: US Army Medical Research and Development Command
Ft. Detrick
Frederick, MD 21702-5012

DISTRIBUTION STATEMENT:

Distribution authorized to U.S. Government agencies only; ~~report contains~~ proprietary information; July 1993. Other requests for this document shall be referred to the U.S. Army Medical Research and Development Command, ATTN: SGRD-RMI-S, Ft. Detrick, Frederick, MD 21702-5012.

REPORT DOCUMENTATION PAGE

Form Approved
OM No 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	1993 July 1	Annual Report (6/1/92-5/31/93)

4. TITLE AND SUBTITLE
Synthesis of Antidotes and Prophylactics for Organophosphorus Acetylcholinesterase Inhibitors

5. FUNDING NUMBERS
Contract No.
DAMD17-92-C-2081

6. AUTHOR(S)
Richard J. Sundberg (Principal Investigator)
Phuoc Van Nguyen (Research Associate)

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Virginia
Department of Chemistry
McCormick Road
Charlottesville, Virginia 22901

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development Command
Fort Detrick
Frederick, Maryland 21702-5012

10 SPONSORING MONITORING AGENCY REPORT NUMBER

11 SUPPLEMENTARY NOTES

12a DISTRIBUTION AVAILABILITY STATEMENT
Distribution authorized to U.S. Government agencies only; ~~report~~ ~~contains~~ proprietary information; July 1993. Other requests for this document shall be referred to the U.S. Army Medical Research and Development Command, ATTN: SGRD-RMI-S, Ft. Detrick, Frederick, MD 21702-5012

12b DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

A series of imidazolylalkyl N,N-dimethylcarbamates was prepared for evaluation of prophylactic and antidotal activity against organophosphorus acetylcholinesterase inhibitors. The series includes the N,N-dimethylcarbamates of 2- and 4-hydroxyalkyl imidazoles, where alkyl is methyl, ethyl or propyl. The final compounds were the 1,3-dimethyl quaternary iodide or tosylate salts. The preparative methods involved reaction of a lithiated imidazole with formaldehyde, oxirane or oxetane to introduce the hydroxyalkyl substituent. For 4-substituted compounds, 2-phenylthioimidazoles were lithiated and subsequently desulfurized with Raney nickel. Both the 3-(N,N-Dimethylcarbamoyloxy) and 4-(N,N-dimethylcarbamoyloxy) derivatives of 1,1-dimethyl-1,2,5,6-tetrahydropyridinium salts were also prepared. No biological data are available at this time.

14. SUBJECT TERMS
Organophosphorus acetylcholinesterase inhibitors
Prophylactic and antidotal activity
Imidazolylalkyl carbamates

15 NUMBER OF PAGES
22

16 PRICE CODE

17 SECURITY CLASSIFICATION OF REPORT	18 SECURITY CLASSIFICATION OF THIS PAGE	19 SECURITY CLASSIFICATION OF ABSTRACT	20 LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Limited

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

✓ Where copyrighted material is quoted, permission has been obtained to use such material.

na Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

✓ Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

✓ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

na For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

Richard J. Kelley 8-10-93

PI Signature Date

Table of Contents

Abstract

A series of imidazolylalkyl N,N-dimethylcarbamates was prepared for evaluation of prophylactic and antidotal activity. The series includes the N,N-dimethylcarbamates of 2- and 4-hydroxyalkyl imidazoles where alkyl is methyl, ethyl and propyl. The final compounds were submitted as quaternary iodide or tosylate salts. The preparative methods involved reaction of a lithiated imidazole with formaldehyde, oxirane or oxetane to introduce the hydroxyalkyl substituent. Both the 3- and 4-(N,N-dimethylcarbamyloxy) derivatives of 1,1-dimethyl-1,2,5,6-tetrahydropyridinium were also prepared. No biological data are available as of this time.

I Introduction

Protective activity against the lethal and incapacitating effect of organophosphorus (OP) acetylcholinesterase (AChE) inhibitors depends upon some appropriate combination of protection and/or reactivation of the enzyme, an anticholinergic agent to counteract the effect of elevated acetylcholine (ACh) levels and, when necessary, an anticonvulsant.[1] Compounds which have prophylactic activity, such as pyridostigmine and physostigmine, act by reversibly blocking the nucleophilic serine at the active site of AChE. Reactivators such as HI-6 are believed to accelerate dephosphorylation of deactivated enzymes. Anticholinergics are necessary to prevent the effects, particularly asphyxiation, of resulting from excessive ACh levels. Anticonvulsants are necessary to prevent or control convulsions which are frequently observed as a secondary effect of OP intoxication.

The purpose of this project is to synthesize and evaluate the prophylactic and antidotal effect of new compounds. The activity was initiated under the auspices of a previous contract, DAMD-17-89-C-9014. That project resulted in the synthesis of a member of aryl-substituted pyridines, imidazoles and imidazo[1,2-a]pyridines with significant prophylactic activity.[2]

The purpose of the present project is to continue to identify new compounds with prophylactic/antidotal activity against OP intoxication. Specific types of compounds which are of interest include pyridines, imidazoles and imidazo[1,2-a]pyridines with new substituent patterns, and other related heterocyclic structures. These efforts are guided primarily by deduction of structural analogies from previously synthesized compounds, but are also guided by the recent publication of detailed structural information of the AChE of *Torpedo* which can provide the basis for more precise structure activity relationships.[3] During the current project period our primary emphasis has been on a series of imidazolylalkyl carbamates.

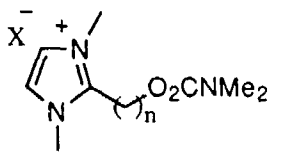
II New Compounds Submitted

The new compounds prepared and submitted during the period 1 June 1992 through 31 May 1993 are shown in Table I.

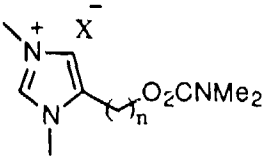
Two of the samples KC012 and KC020 are the phenol precursors of carbamates prepared in the preceding project. These were prepared on the basis of an observation by

Gandour, Quinn and coworkers [4] which showed that the phenol precursor of neostigmine was an active AChE inhibitor.

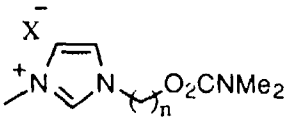
The primary emphasis this year has been on a series of 2- and 4-imidazolylalkyl carbamates, structures **1a-c** and **2a-c**. All except **2a** have been submitted. Work was also begun on the 1-substituted analogs, structures **3a-c**.



	n	X^-
1a	1	OTs
1b (PN68)	2	OTs
1c (PN38)	3	OTs



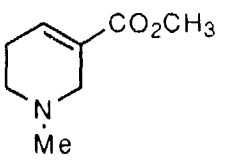
	n	X^-
2a (PN177)	1	I
2b (PN294)	2	I
2c	3	I



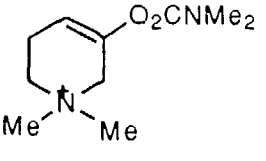
	n	X^-
3a	1	I
3b	2	I
3c	3	I

Interest in this series was the result of antidotal and prophylactic activity exhibited by **1a** (BM03698) and its N-methyl carbamate analog (BM02646). A nonquaternary salt analogous to **1a** (KC005) was also submitted.

Two other samples **4** (PN226) and **5** (PN236) were prepared and submitted. These compounds are structural analogs of pyridostigmine, being tetrahydropyridine derivatives. They are also similar in structure to the muscarinic agonist arecoline and related compounds which are believed to activate cholinergic receptors.

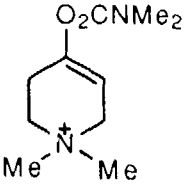


Arecoline



4

PN-226

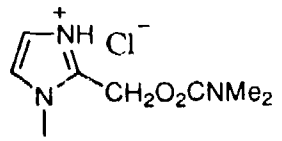
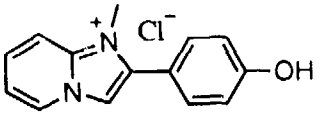
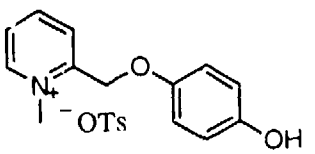
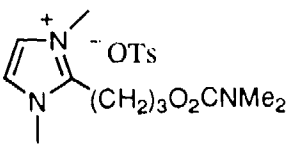
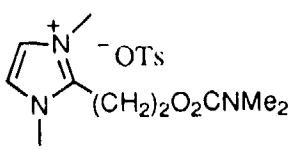
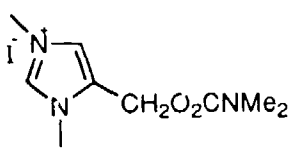
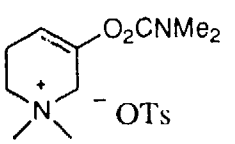
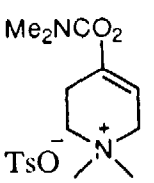
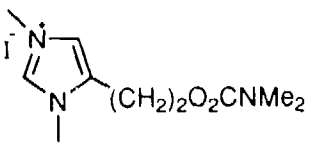


5

PN-236

These compounds are also enol carbamates and should, like aromatic carbamates, be relatively reactive carbamoyl transfer agents.

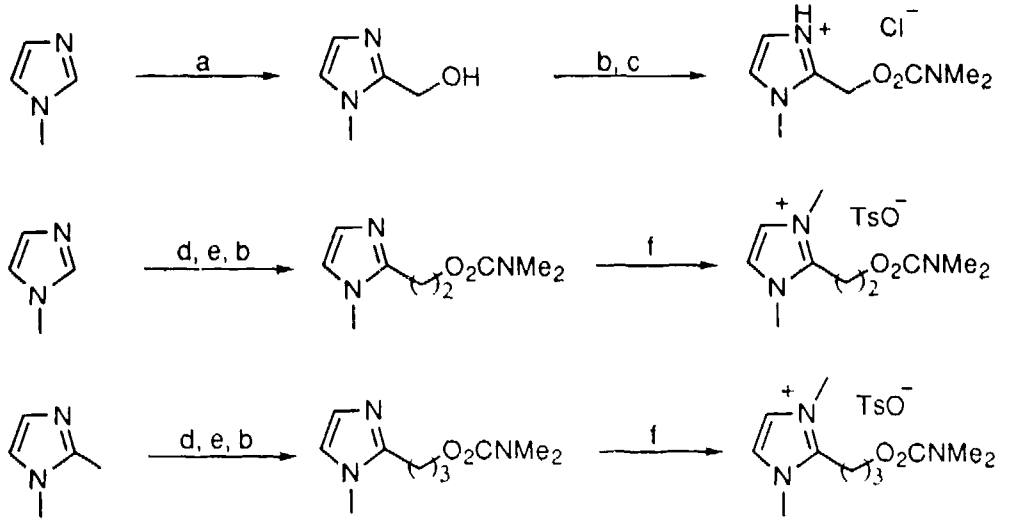
Table I. New Compounds Submitted

Our sample Number	WRAIR Bottle Number	WR Number	Date of Submission	Structure
KC005	BM14299	279314AA	Aug 31 92	
KC012	BM14306	279315AA	Aug 31 92	
KC020	BM14324	279317AA	Aug 31 92	
KC017	BM14315	279316AA	Aug 31 93	
PN38	BM16177	279316AB	Feb 11 93	
PN68	BM16186	279439AA	Feb 11 93	
PN-177	BM17816	279530AA	June 14 93	
PN-226	BM17825	279531AA	June 14 93	
PN-236	BM17834	279532AA	June 14 93	
PN-294	BM17843	279533AA	June 14 93	

III Synthetic Methods

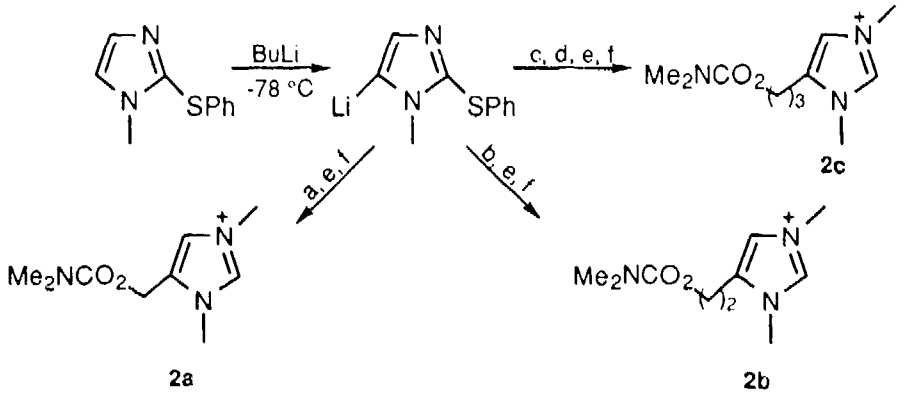
The imidazolylalkyl carbamates **1a-c** and **2a-c** were prepared as indicated in Schemes I and II, respectively. For the most part these methods are known. Lithiation of the imidazole ring is involved in most of the syntheses. While 2-substituted compounds are available by direct lithiation, the 4-substituted analogs required the use of 1-methyl-2-phenylthioimidazole with the 2-phenylthio-substituent serving to block lithiation at the 2-position.

Scheme I



a) CH_2O. b) Me_2NCOCl. c) HCl. d) BuLi. e) Oxirane. f) MeOsT.

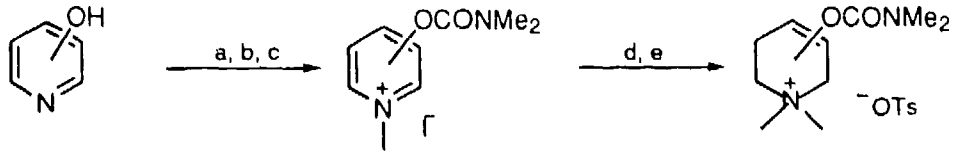
Scheme II



a) $(CH_2O)_n$; Me_2NCOCl. b) Oxirane; Me_2NCOCl. c) Oxetane, BF_3-Et_2O.
d) NaH, DMF; Me_2NCOCl. e) Raney Ni desulfurization. f) MeI.

The tetrahydropyridyl carbamates **4** (PN226) and **5** (PN236) were prepared as shown in Scheme III.

Scheme III



a) NaH, DMF. b) Me_2NCOCl. c) MeI, THF. d) $NaBH_4$, MeOH. e) MeOTs, Et_2O.

IV Biological Results

No *in vivo* results have been obtained for compounds submitted under the current contract. The results for BM03698 and BM02646, which were prepared under the previous contract are summarized in Table II. We have now synthesized most of the N,N-dimethylcarbamates for the 2- and 4-amidazolyl alcohol and are working on the 1-substituted series. We plan to prepare several of the N-methyl carbamates. When the series of structures currently being synthesized is completed (**3a-c**) we will defer preparation of additional imidazolylalkyl carbamates until *in vivo* data is available.

Table II. *In Vivo* Data for BM03698 and BM02646

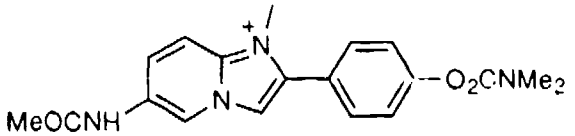
		Per Cent Survival		
	Dose	t - 60 min	t - 15 min	t + 10 min
BM03698	6.25	30	50	40, 50
	25	90	100	100, 70
	100	100	90	80, 20
BM02646	6.25	90	90	70, 50
	25	90	100	90, 80
	100	100	90	80, 60

Preliminary *in vitro* evaluation of **1b** (PN68) and **1c** (PN38) indicate little activity as AChE inhibitors. This is not totally unexpected since, in contrast to substances such as pyridostigmine, these are relatively unreactive alkyl carbamates. A significant point is that should both the *in vivo* protective activity and the *in vitro* inactivity against AChE be confirmed, there would be the strong implication of a non-conventional mode of protective activity.

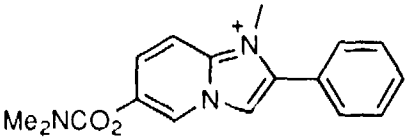
V Plans for Future Work

We plan to complete the current imidazolylalkyl carbamate series within the next quarter. It should also be possible to prepare the corresponding *mono*-carbamates fairly efficiently, since they are derived from the same starting materials. Further work in this area will depend on the biological results. If the activity of these compounds appears promising we will explore other functionalities in addition to the carbamates. Should it prove to be the case that the activity of the compounds is not dependent on reversible carbamoylation we will explore possible alternative mechanisms of activity.

We also expect to begin work on some additional imidazo[1,2-a]pyridine derivatives. In the earlier project most of the carbamate groups were attached at an aryl substituent as in the lead compound BL55142. Only two compounds in which the carbamate group was directly attached to the heterocyclic ring were prepared, as in BM08648, and both were 6-substituted.

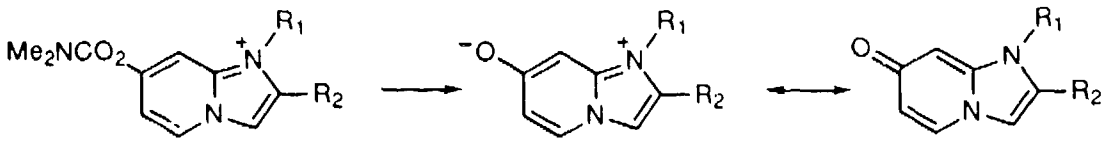


BL55142



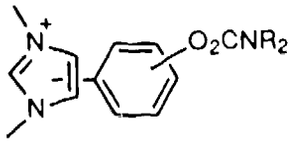
BM08648

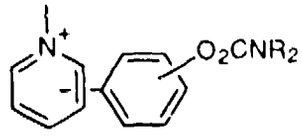
It would be especially interesting to prepare some 7-substituted analogs. Because of the special conjugative stabilization of the product, these could be anticipated to be significantly more reactive than the 6-substituted compounds.



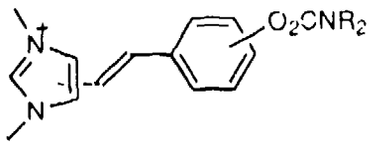
Furthermore, the hydrolysis product would be neutral, whereas in carbamates such as pyridostigmine the product remains cationic. Synthesis of this series of compounds will require development of a workable synthesis of 7-hydroxyimidazo[1,2-a]pyridine since this substitution pattern is rare.

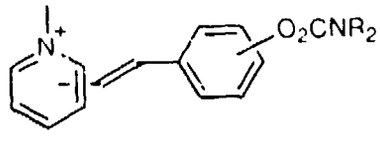
We also plan to initiate work on arylimidazoles and arylpyridines bearing carbamate groups.





Similarly styrylimidazoles and styrylpyridines will be of interest.





These are related to the aryloxy derivatives of imidazole and pyridine prepared in the previous project.[2]

VI Experimental Section

Melting points are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, Georgia. ^{1}H and ^{13}C NMR spectra were obtained at 300 and 75.5 MHz, respectively. Reactions which required anhydrous conditions were carried out under an Ar atmosphere in oven- or flame-dried glassware. Organic solvents were purified by standard techniques prior to use unless used for extractions. All reagents were the best grade commercially available and were used without further purification, unless otherwise noted. 1-Methyl-2-phenylthio-1*H*-imidazole **6** was prepared according to the known procedure[5] (92% yield, colorless liquid, bp 140 °C /0.01 mmHg). All intermediates were used in the next steps without further purification, unless otherwise noted.

1-Methyl-2-hydroxymethyl-1*H*-imidazole[6] (7a)

1-Methyl-1*H*-imidazole (10.9 mL, 0.136 mol) and formaldehyde (37% in water, 18.4 mL, 1.5 equiv) were heated in a pressure bottle for 5 h at 140 °C. The excess water and formaldehyde was removed under reduced pressure and the crude product **7a** obtained as a yellowish oil was used for next reaction without further purification.

1-Methyl-2-(N,N-dimethylcarbamyloxy)methyl-1*H*-imidazole (7b)

To a solution of **7a** in THF were added N,N-dimethylcarbamoyl chloride (6.3 mL, 0.68 mol) and triethylamine (9.5 mL, 0.68 mol). The mixture was refluxed for 16 h. The solvent was removed and the residue was partitioned between water and methylene chloride. The aqueous layer was washed with methylene chloride and the combined organic layer was evaporated to give the crude product **7b** as a thick oil.

1-Methyl-2-(N,N-dimethylcarbamoyloxy)methyl-1*H*-imidazole Hydrochloride 1d (KC005)

7b was dissolved in ether and HCl gas was introduced. After reflux for 1 h a solid precipitate was obtained. The hydrochloride was recrystallized from ethanol/ether to give **1d** as white needle crystals: mp 161-3 °C; IR (KBr) ν_{max} 3405, 3141, 3066, 2935, 1712, 1534, 1400, 1185 cm^{-1}; ^1H NM (D_2O) δ 7.41 (s, 2 H), 5.34 (s, 2 H), 3.88 (s, 3 H), 2.92 (s, 3 H), 2.85 (s, 3 H). Anal. Calcd for $C_8H_{14}ClN_3O_2$: C, 43.74; H, 6.42; N, 19.13; Cl, 16.10. Found: C, 43.60; H, 6.40; N,19.04; Cl, 16.03.

2-(4'-Hydroxyphenyl)imidazo[1,2-a]pyridine

A general procedure was followed in the synthesis of 2-(4'-hydroxyphenyl)-imidazo[1,2-a]pyridine hydrobromide from 2-amino pyridine and α-bromo-4-hydroxy-acetophenone.[7] The resulting salt was suspended in water and excess sodium bicarbonate was added. The mixture was stirred vigorously for 12 h. The product was obtained after filtration and washed with water.

1-Methyl-2-(4'-hydroxyphenyl)imidazo[1,2-a]pyridinium Chloride (KC012)

A general procedure for quaternization[8] was followed, which included methylation with iodomethane and anion anion exchange with Amberlite resin. Recrystallization from hot acetonitrile gave 72% yield of the desired product: mp 233-235 °C; IR (KBr) ν_{max} 3397, 3073, 3051, 1614, 1504, 1282 cm^{-1}; ^1H NMR (D_2O) δ 8.58

(d, 1 H), 7.99 (s, 1 H), 7.89 (m, 2 H), 7.43 (m, 3 H), 6.93 (d, 2 H). Anal. Calcd for $C_{14}H_{13}ClN_2O$. 0.25 H_2O: C, 63.39; H, 5.13; N, 10.57; Cl, 13.37. Found: C, 62.98; H, 5.12; N, 10.61; Cl, 13.34.

1-Methyl-2-(2-hydroxyethyl)-1*H*-imidazole (8a)

A solution of *n*-BuLi in hexane (44 mL, 0.11 mol) was added dropwise via a canula to an ice-cooled (-5 °C) solution of 1-methylimidazole (8.21 g, 0.1 mol, colorless liquid, bp 47°C/0.3mmHg) in dry THF (200 mL). The mixture was stirred at 0°C for 1 h, then ethylene oxide (6.61 g) was slowly added. The mixture was allowed to gradually warm to room temperature and was stirred overnight. The reaction mixture was quenched with cold 10% HCl solution (200 mL). The organic layer was washed with 10% HCl solution (2 x 30 mL). The combined aqueous layers were basified with K_2CO_3, saturated with NaCl and then extracted with $CHCl_3$ (6 x 50 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave a thick yellow oil. Removal of unreacted starting material (2.9 g) by vacuum distillation (Kugelrohr) afforded **8a** as a yellow solid (4.68 g, 57% conversion): ^1H NMR ($CDCl_3$) δ 6.89 (s, 1 H), 6.80 (s, 1 H), 4.00 (t, 2 H, J = 5.6 Hz), 3.57 (s, 3 H), 2.84 (t, 2 H, J = 5.6 Hz); ^{13}C NMR (CDCL3) δ 146.73, 126.59, 120.30, 59.70, 32.44, 28.90.

1-Methyl-2-(2-N,N-dimethylaminocarbonyloxyethyl)-1*H*-imidazole (8b)

NaH (1.1 g, 36.6 mmol, 80% dispersion in mineral oil) was carefully added to a mixture of **8a** (4.2 g, 33.3 mmol) in dry DMF (50 mL) at 0°C. After being stirred for 10 min in an ice-bath, then 30 min at room temperature, the mixture was cooled to 0°C and N,N-dimethylcarbamoyl chloride (4.65 g, 43 mmol) was slowly added by syringe. The ice-bath was removed and the reaction mixture was stirred at room temperature overnight. The mixture was quenched with 1% KOH solution, saturated with NaCl and then extracted with $CHCl_3$ (5 x 50 mL). The organic extract was washed with 5% HCl solution (2 x 150 mL). The cooled combined aqueous layers were basified with 10% KOH solution, saturated with NaCl and then extracted with $CHCl_3$ (6 x 50 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness to give a thick oil **8b** (3.76 g, 57%): ^1H NMR ($CDCl_3$) δ 6.89 (s, 1 H), 6.77 (s, 1 H), 4.36 (t, 2 H, J = 7.2 Hz), 3.58 (s, 3 H), 2.99 (t, 2 H, J = 7.2 Hz), 2.84 (br s, 6 H).

1,3-Dimethyl-2-(2-N,N-dimethylaminocarbonyloxyethyl)-1*H*-imidazolium Tosylate (1b) (PN68)

A mixture of **8b** (0.3 g, 1.57 mmol) and methyl *p*-toluenesulfonate (0.44 g, 2.35 mmol) in dry CH_3CN (10 mL) was stirred at 60°C (bath temperature) for 14 h. The reaction mixture was diluted with CH_3CN and decolorized with charcoal. The volume of organic solvent was reduced under aspirator pressure then ether was added. The resulting mixture was cooled in the freezer to give a crude solid **1b** (0.48 g, 67%) as white crystals from CH_3CN/ether: mp 145- 145.5°C; IR (KBr) ν_{max} 3173, 3088, 1695, 1207 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (d, 2 H, J = 8.0 Hz), 7.53 (s, 2 H,), 7.11 (s, 2 H, J = 8.0 Hz), 4.26 (t, 2 H, J = 6.3 Hz), 3.82 (s, 6 H), 3.42 (t, 2 H, J = 6.3 Hz), 2.81 (s, 3 H), 2.76 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.25, 144.06, 143.89, 138.75, 128.30, 125.48, 122.89, 60.47, 36.27, 35.70, 35.12, 23.81, 20.99. Anal. Calcd for $C_{17}H_{25}N_3O_5S$: C, 53.25; H, 6.57; N, 10.96. Found: C, 53.16; H, 6.59; N, 10.94.

1-Methyl-2-(3-hydroxypropyl)-1*H*-imidazole (9a)

To a cooled (-5°C) solution of 1,2-dimethylimidazole (10.48 g, 0.109 mol) in dry THF (250 mL) was added dropwise a solution of *n*-BuLi in hexane (48 mL, 0.12 mol). The rate of addition was such that the temperature of the mixture remained <0°C. The mixture was stirred at this temperature for 30 min, then ethylene oxide (6 mL, 0.12 mol) was added at such a rate that the temperaute of the mixture was below 10°C. After being stirred at this temperature for an additional 1 h, then at room temperature overnight, the reaction mixture was quenched with 10% HCl solution (300 mL). The organic layer was washed with 10% HCl solution (2 x 50 mL). The combined aqueous layers were basified with K_2CO_3, then extraced with $CHCl_3$ (8 x 50 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness to give a thick yellow oil **9a** (13 g, 85%)): ^1H NMR ($CDCl_3$) δ 6.9 (s, 1 H), 6.76 (s, 1 H), 4.14 (t, 2 H, J = 6.3 Hz), 3.55 (s, 3 H), 2.87 (s, 3 H), 2.72 (t, 2 H, J = 7.6 Hz), 2.06-2.16 (m, 2 H).

1-Methyl-2-(3-N,N-dimethylaminocarbonyloxypropyl)-1H-imidazole (9b)

N,N-Dimethylcarbamoyl chloride (3.6[illegible] g, 34.2 mmol) was added via a syringe to a solution of **9a** (3.2 g, 22.8 mmol) in dry pyridine (20 mL). The reaction mixture was heated to gentle reflux for 30 h, then cooled to room temperature. Water (30 mL) was added and the mixture was stirred for 10 min. The aqueous phase was basified with K_2CO_3, saturated with NaCl, then extracted with $CHCl_3$ (6 x 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and decolorized with charcoal.

Removal of the solvent gave a brown oil **9b** (3.5 g, 73%): ^{1}H NMR ($CDCl_3$) δ 6.9 (s, 1 H), 6.77 (s, 1 H), 4.15 (t, 2H, J = 6.3 Hz), 3.55 (s, 3 H), 2.88 (br s, 6 H), 2.72 (t, 2 H, J = 7.5 Hz), 2.07-2.16 (m, 2 H).

1,3-Dimethyl-2-(3-N,N-dimethylaminocarbonyloxypropyl)-1*H*-imidazolium Tosylate (1c) (PN38)

Quarternization of **9b** (2.03 g, 9.6 mmol) was carried out with MeOTs (2.68 g, 14.4 mmol) in CH_3CN (25 mL) as described earlier to give **1c** (1.75 g, 46%) as colorless needles from CH_3CN/ether: mp 124.5°-125.5°C; IR (KBr) ν_{max}3115, 3082, 1709, 1215, 1182 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.67 (d, 2 H, J = 8.1 Hz), 7.54 (s, 2 H), 7.11 (d, 2 H, J = 8.1 Hz), 4.04 (t, 2 H,J = 5.8 Hz), 3.82 (s, 6 H), 3.11 (t, 2 H, J = 7.6 Hz), 2.86 (s, 3H), 2.79 (s, 3 H), 2.32 (s, 3 H), 1.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 155,.76, 146.17, 144.18, 138.80, 128.35, 125.59, 122.81, 63.41, 36.29, 35.72, 35.11, 25.83, 21.07, 20.12. Anal. Calcd for $C_{18}H_{27}N_3O_5S$: C, 54.39; H, 6.85; N, 10.57; S, 8.06. Found: C, 54.21; H, 6.92; N, 10.52; S, 7.99.

1-Methyl-2-phenylthio-5-(N,N-dimethylcarbamyloxy)methyl-1*H*-imidazole (10a)

To a cooled solution (-78 °C) of 1-methyl-2-phenylthio-1*H*-imidazole **6** (1.9 g, 10 mmol) in dry THF (40 mL) was added dropwise a solution of *n*-BuLi in hexane (4 mL, 10 mmol). The mixture was stirred for 30 min, then predried paraformaldehyde (0.45 g, 15 mmol) was added. The mixture was stirred at -78 °C for 15 min and allowed to warm up slowly. The temperature of the reaction mixture was maintained at 10-15 °C using an ice bath until the color of the mixture changed from orange to milky white (about 30 min). The reaction mixture was then cooled to 0 °C and N,N-dimethylcarbamyl chloride (1.6 g, 15 mmol) was added dropwise. The mixture was stirred at room temperature for 1 h then quenched with cold aqueous solution of 10% HCl (40 mL) and extracted with ether (2 x 15 mL). The aqueous phase was basified with 20% KOH solution, saturated with NaCl and extracted with EtOAc (6 x 50 mL). The organic layers were washed with brine and dried (Na_2SO_4). Removal of solvent gave **10a** (2.5 g, 86%) as a thick oil: ^{1}H NMR ($CDCl_3$) δ 7.18-7.30 (m, 6 H), 5.10 (s, 2 H), 3.63 (s, 3 H), 2.93 (s, 3 H), 2.86 (s, 3 H).

1-Methyl-5-(N,N-dimethylcarbamyloxy)methyl-1*H*-imidazole (10b)

A mixture of **10a** (1.17 g, 4 mmol) and Raney Nickel (ca. 4.7 g, W-2 in ethanol) in ethanol/acetone was stirred at room temperature for 15 min. The solvent was carefully decanted and the solid nickel residue was washed with EtOH (2 x 50 mL), then CH_2Cl_2 (2 x 50 mL). The combined organic phase was evaporated to dryness to give a residue which was redissolved in $CHCl_3$. The mixture was dried ($MgSO_4$) and filtered (Celite). Removal of solvent gave **10b** (0.414 g, 56%) as colorless solid: ^{1}H NMR ($CDCl_3$) δ 7.45 (s, 1 H), 7.10 (s, 1 H), 5.10 (s, 2 H), 3.67 (s, 3 H), 2.93 (s, 3 H), 2.87 (s, 3 H).

1,3-Dimethyl-4-(N,N-dimethylcarbamyloxy)methyl-1*H*-imidazolium Iodide (2a) (PN-177)

A mixture of **10b** (0.36 g, 1.96 mmol) and methyl iodide (0.97 mL, 15 mmol) in dry THF (8 mL) was stirred at 60 °C for 2 h. The solvent was then removed under reduced pressure. The resulting yellow oil was dissolved in H_2O (5 mL). The aqueous solution was then washed with $CHCl_3$ (3 x 4 mL), ether (4 mL) and evaporated to dryness to afford a thick, yellow oil **2a** (0.8 g, 82%) which gave a white solid on crystallization with acetone/ether: mp 105.5 - 6.5 °C; IR (KBr) ν_{max} 3109, 3061, 1709, 1188 cm^{-1}; ^{1}H NMR (DMSO) δ 9.14 (s, 1 H), 7.80 (s, 1 H), 5.14 (s, 2 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 2.83 (s, 3 H), 2.81 (s, 3 H); ^{13}C NMR (DMSO) δ 154.60, 137.81, 129.82, 123.29, 54.68, 36.16, 35.89, 35.60, 33.79. Anal. Calcd for $C_9H_{16}O_2N_3I$: C, 33.25; H, 4.96; N, 12.92. Found: C, 33.31; H, 4.94; N, 12.83.

1-Methyl-2-phenylthio-5-[2-(N,N-dimethylcarbamyloxy)ethyl]-1*H*-imidazole (11a)

n-BuLi in hexane (4.4 mL, 11 mmol) was added to a solution of **6** (1.9 g, 10 mmol) in dry THF (50 mL) at -78 °C. The mixture was stirred for 30 min, then pre-cooled ethylene oxide (0.9 g, 20 mmol) was added. After being allowed to warm to room temperature overnight the reaction mixture was cooled in an ice-bath, then N,N-dimethylcarbamyl chloride (1.61 g, 15 mmol) was added via a syringe. The mixture was stirred at room temperature for 14 h, then diluted with ether (20 mL) and quenched with cold 10% HCl solution. The organic phase was separated and washed with 10% HCl solution (2 x 15 mL). The combined aqueous layers were basified with cold 20% KOH solution to pH = 10, and extracted with EtOAc (4 x 50mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Removal of solvent gave **11a** (2.9 g, 95%) as a thick oil: ^{1}H NMR ($CDCl_3$) δ 7.11-7.28 (m, 5 H), 7.04 (s, 1 H), 4.29 (t, 2 H, J = 6.9 Hz), 3.56 (s, 3 H), 2.8-2.95 (overlapped m, 8 H).

1-Methyl-5-[2-(N,N-dimethylcarbamyloxy)ethyl]-1*H*-imidazole (11b)

Desulfurization of **11a** (1.5 g, 5 mmol) with Raney Ni (ca. 5.8 g ,W-2 in ethanol) in absolute EtOH (30 mL) following the procedure described for **10a** gave **11b** (0.84 g, 85%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.39 (s, 1 H), 6.87 (s, 1 H), 4.27 (t, 2 H, J = 6.9 Hz), 3.60 (s, 3 H), 2.84-2.93 (overlapped m, 8 H); ^{13}C NMR ($CDCl_3$) δ 156.27, 137.77, 128.04, 127.26, 63.29, 36.34, 35.81, 31.21, 24.06.

1,3-Dimethyl-4-[2-(N,N-dimethylcarbamyloxy)ethyl]-1*H*-imidazolium Iodide (2b) (PN-294)

Quarternization of **11b** (0.33 g, 1.67 mmol) was carried out with methyl iodide (0.83 mL, 13.4 mmol) in THF (5 mL) as described previously to give **2b** as a thick, pale yellow oil: ^{1}H NMR (DMSO) δ 8.98 (s, 1 H), 7.54 (s, 1 H), 4.20 (t, 2 H, J = 6.4 Hz), 3.81 (s, 3 H), 3.77 (s, 3 H), 2.99 (t, 2 H, J = 6.4 Hz), 2.81 (s, 6 H); ^{13}C NMR (DMSO) δ 155.27, 136.63, 131.89, 120.68, 61.86, 36.00, 35.70, 35.55, 33.31. Anal. Calcd for $C_{10}H_{18}O_2N_3I.1/2\ H_2O$: C, 34.49; H, 5.50; N, 12.06. Found: C, 34.48; H, 5.51; N, 11.97.

1-Methyl-2-phenylthio-5-(3-hydroxypropyl)-1*H*-imidazole (12a)

To a solution of **6** (4.1 g, 21.54 mmol) in dry THF (45 mL) at -78 °C was added dropwise a solution of *n*-BuLi in hexane (9.05 mL, 22.62 mmol). After being stirred at -78 °C for 30 min, the mixture was added via canula to a precooled (-78 °C) solution of oxetane (1.25 g, 21.5 mmol) and BF_3-OEt_2 (3.97 mL, 32.3 mmol) in dry THF (50 mL). The reaction mixture was stirred at -78 °C for 2 h and warmed up to room temperature overnight. Work up as usual gave a crude product **12a** (2.37 g, 44%) as a dark yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.01-7.28 (m, 5 H), 6.93 (s, 1 H), 3.71 (t, 2 H, J = 6.2 Hz), 3.49 (s, 3 H), 3.26 (br s, 1 H), 2.65 (t, 2 H, J = 7.9 Hz), 1.89 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 129.16, 127.48, 127.01, 125.94, 61.17, 31.02, 30.63, 21.48.

1-Methyl-2-phenylthio-5-[3-(N,N-dimethylcarbamyloxy)propyl]-1*H*-imidazole (12b)

Carbamylation of the crude **12a** (2.37 g, 9.57 mmol) in DMF (25 mL) with sodium hydride (0.32 g, 10.55 mmol, 80% dispersion in mineral oil) and N,N-dimethylcarbamyl chloride (1.15 mL, 12.44 mmol) as described previously with **8a** gave a thick oil which was purified by column chromatography (silica gel, gradient elution, 50-0% of hexane in EtOAc) to afford **12b** (0.663 g, 22%) as a thick yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.11-7.27 (m, 5 H), 6.98 (s, 1 H), 4.16 (t, 2 H, J = 6.3 Hz), 3.52 (s, 3 H), 2.91

(br s, 6 H), 2.64 (t, 2 H, J = 7.7 Hz), 1.91-2.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 156.00, 136.51, 134.91, 134.51, 128.78, 127.20, 126.99, 125.95, 63.88, 38.16, 35.97, 35.45, 30.67, 27.04, 21.43.

1-Methyl-5-[3-(N,N-dimethylcarbamyloxy)propyl]-1*H*-imidazole (12c)

Desulfurization of **12b** (0.85 g, 2.68 mmol) with Raney Nickel (3.15 g, 53.6 mmol) in EtOH as described previously gave **12c** (0.214 g, 37.8%) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 7.37 (s, 1 H), 6.79 (s, 1 H), 4.15 (t, 2 H, J = 6.3 Hz), 3.56 (s, 3 H), 2.91 (s, 6 H), 2.63 (t, 2 H, J = 7.6 Hz), 1.93-2.02 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 156.19,137.28, 130.82, 125.90, 64.08, 36.07, 35.52, 30.85, 27.59, 20.22.

1,3-Dimethyl-4-[3-(N,N-dimethylcarbamyloxy)propyl]-1*H*-imidazolium Iodide (2c)

Quarternization of **12c** (95 mg, 0.45 mmol) with methyl iodide (0.14 mL, 2.25 mmol) in THF (3 mL) as previously described gave a white solid **2c** (134 mg, 85%): mp 115-6 °C from acetone/ether; IR (KBr) ν_{max} 3172, 1701, 1188 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.00 (s, 1 H), 7.22 (s, 1 H), 4.18 (t, 2 H, J = 6.2 Hz), 4.04 (s, 3 H), 3.96 (s, 3 H), 2.74 (t, 2 H, J = 7.5 Hz), 1.99-2.09 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 137.30, 135.06, 119.86, 63.28, 36.83, 36.45, 36.01, 34.21, 28.82, 20.23. Anal. Calcd for $C_{11}H_{20}O_2N_3I$: C, 37.40; H, 5.70; N, 11.89. Found: C, 37.45; H, 5.74; N, 11.81.

3-(N,N-Dimethylcarbamyloxy)pyridine (13a)

Sodium hydride (3.3 g, 0.11 mol, 80% dispersion in mineral oil) was added in small portions to an ice-cooled solution of 3-pyridinol (9.51 g, 0.1 mol) in DMF (70 mL). The mixture was stirred in an ice bath for 10 min, then at room temperature for 30 min. The mixture was cooled and N,N-dimethylcarbamyl chloride (0.13 mol, 11.96 mL) was added via syringe. The reaction mixture was then stirred at 80 °C for 2 h, cooled and poured into cold aqueous 1% KOH solution. The mixture was saturated with NaCl then extracted with benzene:petroleum ether (4:1) (3 x 80 mL). The combined organic layers were washed with H_2O (150 mL), then extracted with 5% HCl solution (3 x 75 mL). The cooled aqueous phase was basified with 20% KOH solution and extracted with benzene:petroleum ether (4:1) (3 x 80 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Removal of solvent gave a pale yellow liquid **13a** (11.05 g, 66.4%): ^1H NMR ($CDCl_3$) δ 8.43-8.45 (br s, 1 H), 7.51 (ddd, 1 H, J = 1.3 Hz, J = 2.5 Hz, J = 8.3 Hz), 7.30 (dd, 1 H, J = 4.7 Hz, J = 8.3 Hz), 3.12 (s, 3 H), 3.02 (s, 3 H): ^{13}C NMR ($CDCl_3$) δ 154.48, 148.03, 146.10, 143.48, 129.16, 123.52, 36.65, 36.35.

1-Methyl-3-(N,N-dimethylcarbamyloxy)pyridinium Iodide (13b)

A mixture of **13a** (9.8 g, 58.97 mmol) and methyl iodide (7.3 mL, 118 mmol) in dry THF (50 mL) was magnetically stirred overnight. The resulting precipitate was filtered and recrystallized with acetone/ether to give **13b** as a white solid (14.25 g, 78.4%): ^{1}H NMR ($CDCl_3$) δ 8.83 (s, 1 H), 8.68 (d, 1 H, J = 6.0 Hz), 8.37 (d, 1 H, J = 8.7 Hz), 8.03-8.08 (dd, 1 H, J = 6.0 Hz, J = 8.7 Hz), 4.76 (DO-H), 4.40 (s, 3 H), 3.13 (s, 3 H), 3.00 (s, 3 H).

1-Methyl-1,2,5,6-tetrahydro-3-(N,N-dimethylcarbamyloxy)pyridine (13c)

To an ice-cooled solution of **13b** (1.54 g, 5 mmol) in MeOH (25 mL) was added $NaBH_4$ (0.75 g, 20 mmol) in small portions. The mixture was stirred in an ice bath for 30 min, then at room temperature for 1 h. The volume of solvent was carefully reduced and H_2O (10 mL) was added. The solution was saturated with NaCl then extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL) and dried ($MgSO_4$). Removal of solvent gave a pale yellow liquid **13c** (0.86 g, 96.6%): ^{1}H NMR ($CDCl_3$) δ 5.44 (ca. 1 H), 3.02 (dd, 2 H, J = 2.4 Hz, J = 3.9 Hz), 2.95 (s, 3 H), 2.93 (s, 3 H), 2.54 (t, 2 H, J = 5.9 Hz), 2.38 (s, 3 H), 2.23-2.29 (br m, 2 H); ^{13}C NMR ($CDCl_3$) δ 145.84, 110.97, 55.13, 51.23, 45.21, 36.46, 36.30, 24.04.

1,1-Dimethyl-1,2,5,6-tetrahydro-3-(N,N-dimethylcarbamyloxy)pyridinium Tosylate (4) (PN-226)

A mixture of **13c** (0.85 g, 4.78 mmol) and methyl tosylate (1.78 g, 9.57 mmol) in ether (5 mL) was stirred at room temperature for 1 h. The precipitate was filtered and washed several times with ether to give **4** (1.63 g, 93%), as white solid from CH_3CN/ether: mp 146-7 °C; IR (KBr) ν_{max} 3040, 3028, 1718, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2 H, J = 7.9 Hz), 7.14 (d, 2 H, J = 7.9 Hz), 5.61 (t, 1 H, J = 3.4 Hz), 4.04 (br s, 2 H), 3.75 (t, 2 H, J = 6.1 Hz), 3.41 (s, 6 H), 2.92 (s, 3 H), 2.89 (s, 3 H), 2.50 (br m, 2 H), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.66, 143.82, 139.50, 139.11, 128.56, 125.70, 110.77, 60.55, 57.91, 51.65, 36.49, 36.32, 21.18, 19.96. Anal. Calcd for $C_{17}H_{30}O_5N_2S$: C, 55.12; H, 7.07; N, 7.56. Found: C, 55.19; H, 7.10; N, 7.61.

1-Methyl-4-(N,N-dimethylcarbamyloxy)pyridinium Iodide (14b)

To an ice-cooled solution of 4-hydroxypyridine (4.75 g, 50 mmol) in dry DMF (70 mL) was added NaH (1.65 g, 55 mmol) in small portions. After being stirred at room

temperature for 30 min, the mixture was cooled in an ice bath and N,N-dimethylcarbamyl chloride (10.75 g, 0.1 mol) was added slowly via a syringe. The reaction mixture was then stirred at 80 °C for 5 h, cooled and quenched with H_2O (30 mL) followed by aqueous 10% HCl solution (50 mL), saturated with NaCl, then extracted with CH_2Cl_2 (3 x 30 mL). The aqueous phase was basified with 20% NaOH solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and filtered through a short column of silica gel. Removal of the solvent gave **14a** as a yellow liquid (3.53g, 42%): ^{1}H NMR ($CDCl_3$) δ 8.57 (d, 2 H, J = 4.8 Hz), 7.13 (d, 2 H, J = 4.8 Hz), 3.10 (s, 3 H), 3.02 (s, 3 H).

A mixture of **14a** (0.86 g, 5.18 mmol) and methyl iodide (0.64 mL) in dry THF (10 mL) was stirred at room temperature overnight. The precipitate was filtered and recrystallized with methanol/ether to give **14b** (1.50 g, 94%): mp 149-150 °C (lit.[9] 131-132 °C).

1-Methyl-1,2,5,6-tetrahydro-4-(N,N-dimethylcarbamyloxy)pyridine (14c)

Following the procedure described for **13c**, the reduction of **14b** (1.17 g, 3.8 mmol) with $NaBH_4$ (0.58 g, 15,2 mmol) in methanol (15 mL) gave **14c** as a liquid (0.65 g, 96%): ^{1}H NMR ($CDCl_3$) δ 5.32-5.37 (ca, 1 H), 3.02 (ddd, 2 H, J = 2.7 Hz, J = 3.5 Hz, J = 9.2 Hz), 2.93 (br s, 6 H), 2.65 (dd, 2 H, J = 5.7 Hz, J = 12.3 Hz), 2.30-2.40 (overlapped, 5 H); ^{13}C NMR ($CDCl_3$) δ 154.53, 146.85, 111.04, 52.77, 51.75, 45.02, 36.29, 36.20, 27.74.

1,1-Dimethyl-1,2,5,6-tetrahydro-4-(N,N-dimethylcarbamyloxy)pyridinium Tosylate (5) (PN-236)

To a solution of **14c** (0.63 g, 3.53 mmol) in dry CH_3CN (20 mL) was added methyl tosylate (1.316 g, 7.00 mmol). After being stirred at room temperature for 2 h, the reaction mixture was warmed on a steam bath and ether was added. The reaction mixture was then cooled on an ice bath to give a white solid **5** (1.07 g, 83%): mp. 159-9.5 °C from CH_3CN/ether; IR (KBr) ν_{max} 3032, 3022, 1718, 1190 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2 H, J = 7.9 Hz), 7.14 (d, 2 H, J = 7.9 Hz), 5.33 (br s, 1 H), 4.16 (br d, 2 H, J = 3.0 Hz), 3.78 (t, 2 H, J = 6.5 Hz), 3.41 (s, 6 H), 2.95 (s, 3 H), 2.92 (s, 3 H), 2.56 (br m, 2 H), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.64, 145.40, 143.79, 139.22, 128.67, 125.71, 106.53, 60.02, 58.65, 51.23, 36.50, 36.34, 23.85, 21.20. Anal. Calcd for $C_{17}H_{30}O_5N_2S$: C, 55.12; H, 7.07; N, 7.56. Found: C, 55.12; H, 7.12; N, 7.53.

Acknowledgment. This research was carried out under the auspices of Walter Reed Army Institute of Research, Medical Research and Development, Contract DAMD-17-92-C-2081.

References

1) Harris, L. W.; Stitcher, D. L.; Heyl, W. C. *Life Sci.* **1980**, *26*, 1885-1891; Albuquerque, E. X.; Alkondon, M.; Desphande, S. S.; Cintra, W. M.; Aracava, Y.; Brossi, A. *Int. Congres. Series, Excerpta Med.* **1988**, *832*, 349-373
2) Sundberg, R. J.; Dalvie, D.; Cordero, J.; Mussalam, H. A. *Chem. Res. Toxicol.* **1993**, *6*, 506. Sundberg, R. J.; Dalvie, D.; Cordero, J.; Sabat, M.; Mussallam, H. A. *Chem. Res. Toxicol.* **1993**, *6*, 500.
3) Sussman, J. L.; Harol, M.; Froloro, F.; Oefner, C.; Goldman, A.; Toker, L.; Silman, I. *Science* **1991**, *253*, 872-879.
4) Lee, B. H.; Stelly, T. C.; Colucci, W. J.; Garcia, J. G.; Gandour R. D.; Quinn, D. M. *Chem. Res. Toxicol.* **1992**, *5*, 411.
5) Ohta, S.; Yamamoto, T.; Kawasaki, I.; Yamashita, M.; Katsuma, H.; Nasako, R.; Kobayashi, K.; Ogawa, K. *Chem. Pharm. Bull.* **1992**, *40*, 2681.
6) Jones, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 383; Grindley, R.; Pyman, F. L. *J. Chem. Soc.* **1927**, 3128.
7) Sundberg, R. J.; Dahlhausen, D. S.; Manikumar, G.; Mavunkel, B.; Biswas, A.; Srinivasan, V.; King Jr., F. ; Waid, P. *J. Heterocycl. Chem.*, **1988**, *25*, 129.
8) Noyce, D. S.; Stowe, G. T.; Wong, W. *J. Org. Chem.* **1974**, *39*, 2301; Dreger, E. E. *Org. Syn. Coll. I* **1932**, 306.
9) Zhao, Z.; Dalvie, D.; Naiman, N.; Castagnoli, K.; Castagnoli Jr., N. *J. Med. Chem.* **1992**, *35*, 4473.

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 21 Apr 97

MEMORANDUM FOR Administrator, Defense Technical Information Center, ATTN: DTIC-OCP, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for Contract Number DAMD17-92-C-2081. Request the limited distribution statement for Accession Document Numbers ADB188021, ADB200784, ADB175882, and ADB211649 be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Judy Pawlus at DSN 343-7322.

FOR THE COMMANDER:

per Pawlus Rinehart
GARY R. GILBERT
Colonel, MS
Deputy Chief of Staff for
Information Management

Completed
1-10-00
B.W